RESEARCH PROPOSAL

Synthesis, Characterization and Application of New Cordination Compounds with Nitrogen Heterocyclic Carbenes

For registration to the degree of Doctor of Philosophy

IN THE FACULTY OF SCIENCE

IIS (Deemed to be University), JAIPUR

Submitted by

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Introduction and Review of Literature

N- Heterocyclic Carbenes (NHC)

Carbene belongs to the most reactive species in organic synthesis. A multitude of useful and well-established organic reactions proceed via the intermediate formation of the carbene or carbenoids. Over the last few decades, stable carbenes have received a great deal of attention from a number of researchers.[1]

N- Heterocyclic carbenes are neutral species containing a carbene carbon and at least one adjacent nitrogen atom within a ring structure. In addition to the nitrogen atom, NHC's could be marked by the presence of other heteroatoms (sulphur and oxygen).
N- Heterocyclic carbenes are electronically (orbital overlap) and sterically (Me vs Ad) stabilized.

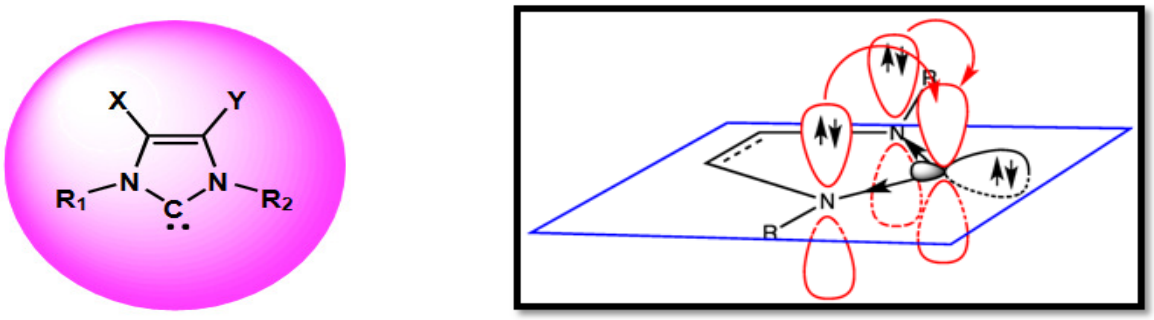
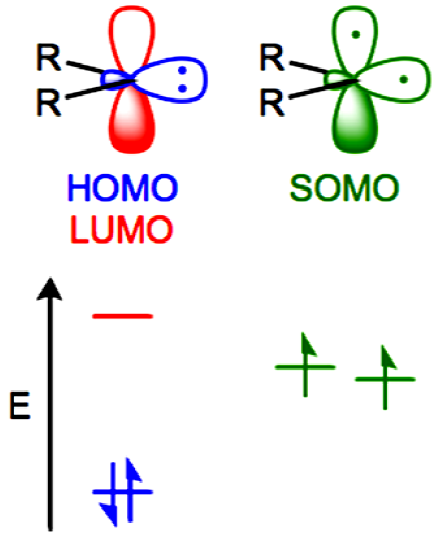


Fig .1

Nitrogen-heterocyclic carbenes (NHCs) constitute a special class of stable carbenes. Due to their steric and electronic properties, N-heterocyclic carbenes (NHCs) attracted much attention and this research area rapidly expanded. These species have been employed in various fields including organocatalysis and organometallic [2]chemistry. Coordination of NHC ligands is not only limited to the transition metals, but there is an expanding range of examples in which NHCs have been used in combination with elements of groups 1, 2, 13, 14, 15, 16, 17 and also the lanthanides. NHCs are strong σ donor ligand and can attack on electron deficient species.[3]

NHCs can complex with low valent and high valent transition metals, alkaline earth metals, and lanthanides (Yt and Sc)[4] N-Heterocyclic carbenes both stabilize and activate metal centers in quite different key catalytic steps of organic syntheses, for example, C-H activation, C-C, C-H, C-O, and C-N bond formation.[5]

General Properties - In general, we can classify carbenes according to the nature of the two non-bonding electrons—if they are spin paired (one up and one down), the carbene is called a singlet; if their spins are parallel, we call the carbene a triplet. Whether a carbene is in the singlet or triplet state depends primarily on the difference in energy between its frontier orbitals—when the FMOs are close in energy, single occupation of each FMO (the triplet state) is likely. As the energy difference increases, the singlet state becomes more likely because the higher-energy FMO is less likely to be occupied.[6]



FMO pictures for singlet and triplet carbenes.

Fig.2

Ground-state spin multiplicity dictates a carbene's reactivity.

- Singlet carbenes have a filled and vacant orbital = possess ambiphilic character.
- Triplet carbenes can be regarded as diradicals.
- Influence of substituents on the carbene will have large effects - ***electronics and sterics.***
- Electron-withdrawing substituents favor the singlet state over the triplet.
- Electron-withdrawing substituents inductively stabilize the nonbonding orbital by increasing its s character and leaving the p-orbital unchanged.
- Electron-donating substituents induce a smaller s-p gap, favoring a triplet state[7]

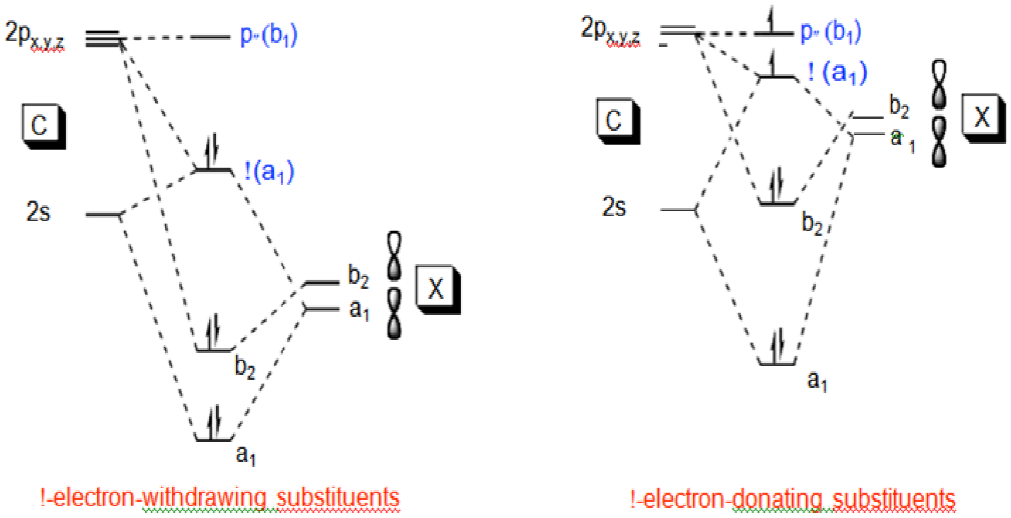


Fig.3

- Bulky substituents kinetically stabilize all types of carbenes.
- If electronic effects are insignificant, steric effects can dictate the ground-state spin multiplicity.
- A linear geometry favors the triplet state, a bent geometry favors the singlet state.[8]

An extensive literature survey has been done on the complexation of N-heterocyclic carbenes with a variety of metals (T.M and main group elements). However, only two reports could be found on the tin complexes with NHCs as ligands.

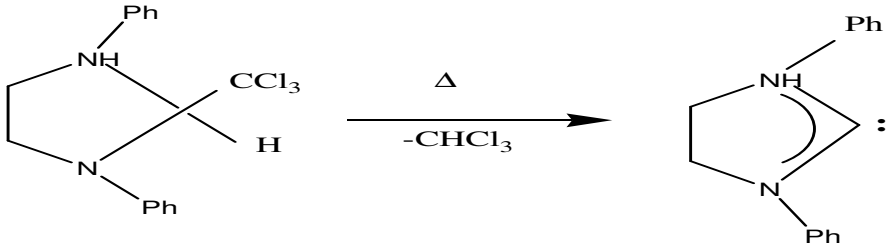
The literature survey is divided into two sections:

2.1) Synthesis of NHC and its metal complexes

2.2) Applications of these complexes in biological field

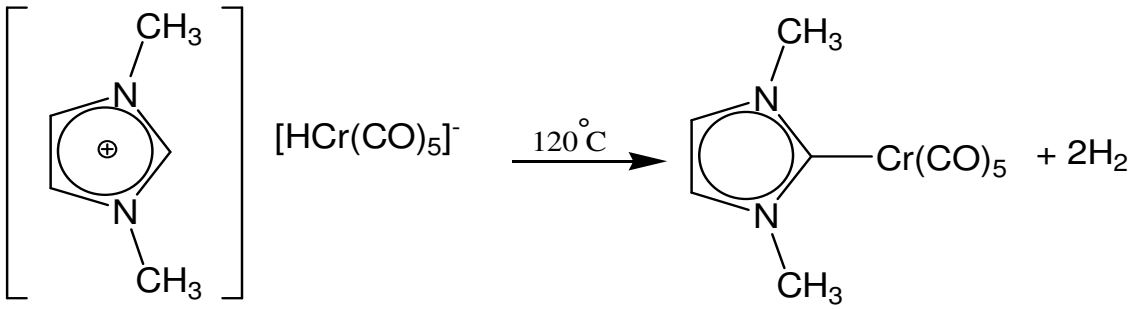
2.1 Synthesis of NHC and its metal complexes

- Wanzlick et *al*. reported the synthesis of an NHC based on imidazolidine that readily dimerized and they proposed that the free form and its dimer are in an equilibrium ("Wanzlick-equilibrium")[9]



Scheme 1. Formation of 1,3-diphenylimidazolidin-2-ylidene

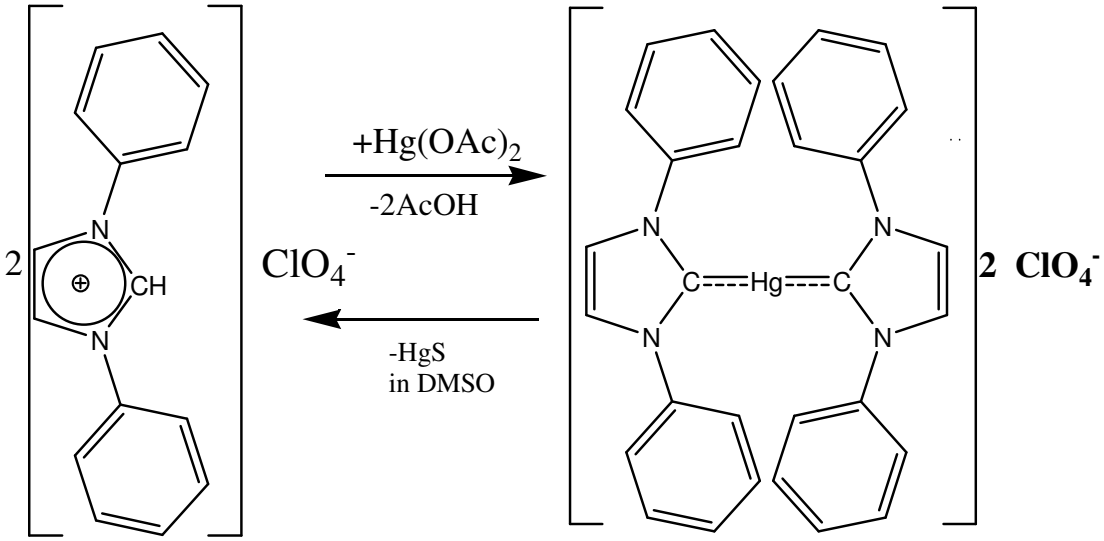
- In 1968, Ofele noted following side reaction when he was working on heterocyclic salts.[10]



Light yellow crystalline solid

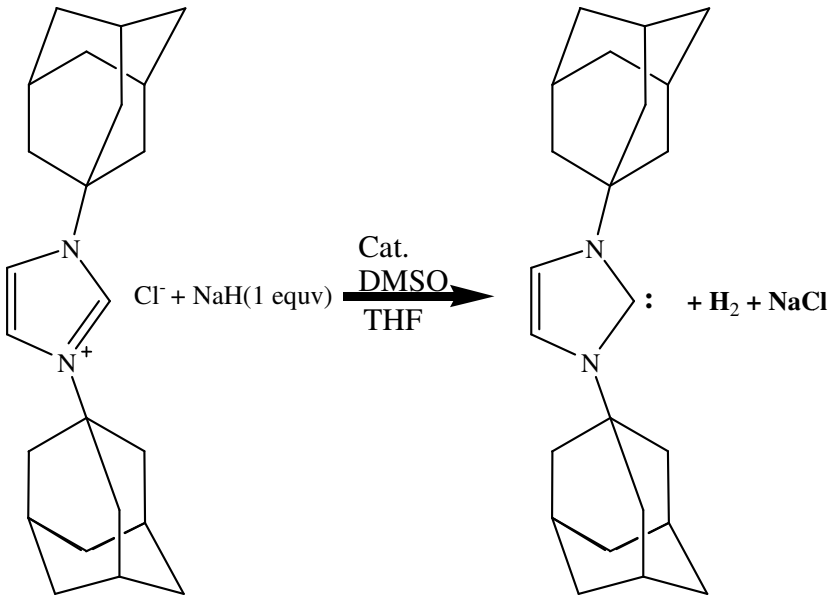
Scheme 2.

- In the same year Wanzlick directly synthesized following compound from nucleophilic carbene.[11]

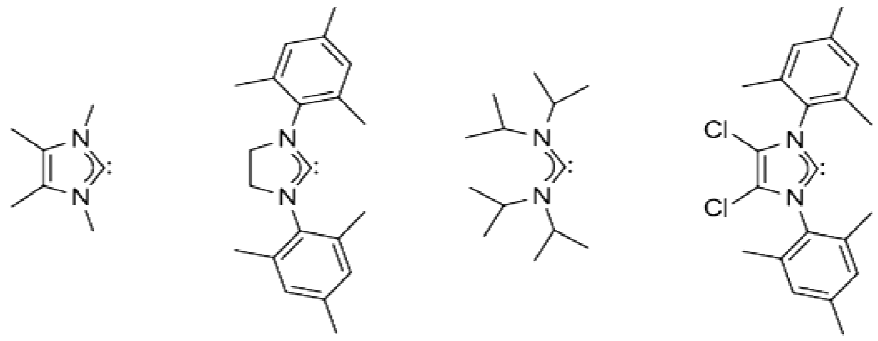


Scheme 3.

- First stable crystalline carbene was reported by Arduengo et *al.* in 1961 by using substituted imidazolinium salts (sterically demanding adamantyl-group) .The targeted isolation by deprotonation of the imidazolium chloride (**1**) with sodium hydride succeeded and they reported "a stable crystalline carbene" (Scheme 5). Arduengo synthesized a series of intriguing NHCs. A fundamental assumption was that the NHCs gained substantial stabilization of an aromatic ground state of the imidazole ring system.[12]



Scheme 4.



(a) without sterically demanding substituent (b) with a saturated back bone (c) acyclic (d) air stable.

Fig. 4

NHCs as ligands in metal complexes

- In 1995, Herrmann et *al.* reported the first catalytic application of an NHC-palladium complex.[13]
- In 2005, Grubbs synthesized ruthenium based Grubbs catalyst and was awarded the Nobel prize in Chemistry.[14]

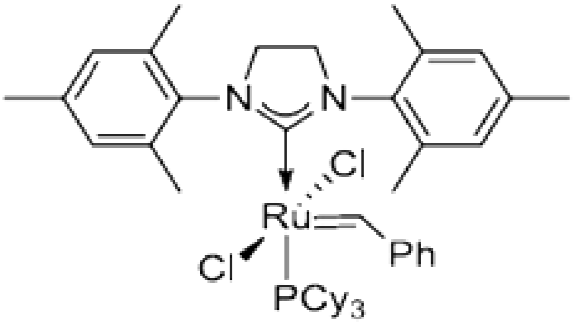
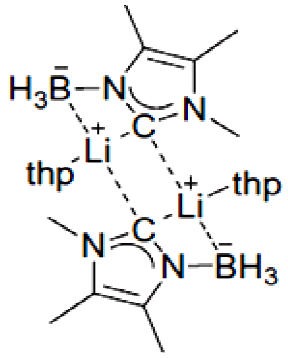


Fig.5

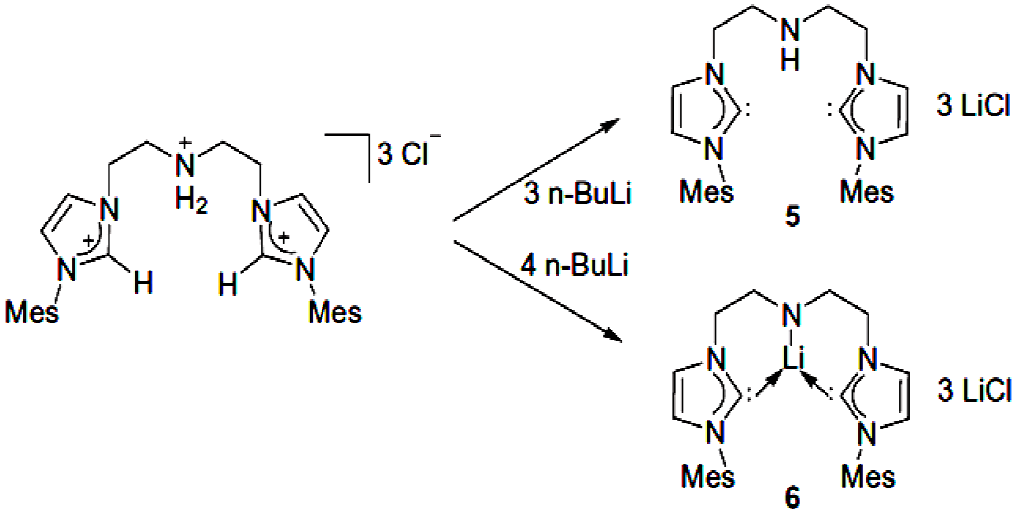
- In 1998, Siebrt and co-workers reported a 3-borane-1,4,5-trimethylimidazol-2-ylidene (1) which was formed through deprotonation of 3-borane-1,4,5-trimethylimidazole using *n*-butyl lithium. The authors described this as a Li(thp)þ1_ (thp=tetrahydropyran) salt, and the solid state structure revealed dimeric units of two carbene centres connected by two lithium ions [15]



$(Li(thp)^{+}\ 1^{-})_2$

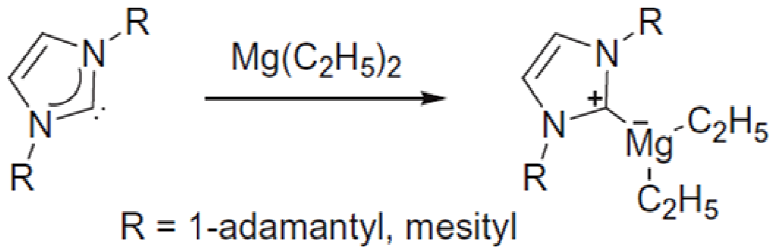
Fig.6

- Arnold and co-workers also reported the synthesis of lithium complexes of the neutral and anionic salts of a tridentate amino biscarbene ligand. Treatment of the cationic amino bis-imidazolium salt with three equivalents of n-butyl lithium affords the lithium amino bis-carbene chloride complex (5). Deprotonation with four equivalents of n-butyl lithium affords the lithium amide salt (6).[16]



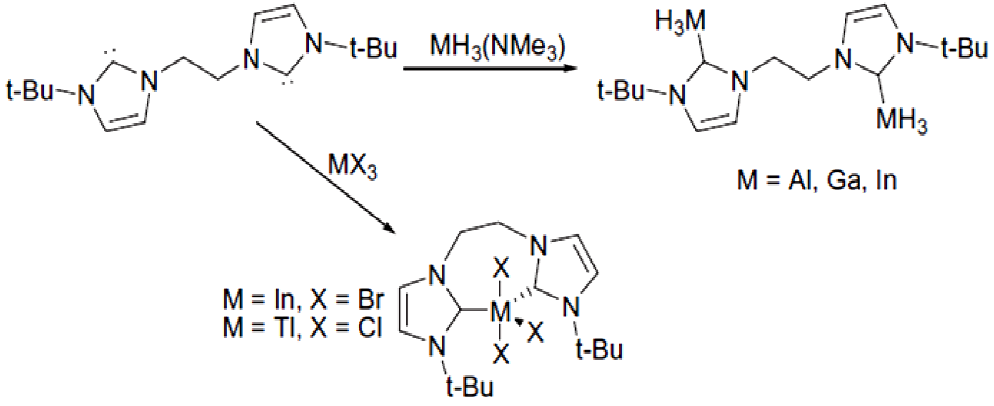
Scheme 5.

- Arduengo et *al.* in 1993 reported first Magnesium-NHC adduct. Single crystal X-ray structures revealed that the N-adamantyl-substituted carbene complex has a monomeric solid state structure, while the less bulky N-mesityl complex is dimeric in the solid state.[17]



Scheme 6.

- In 2002, Jones and co-workers reported bidentate NHC complexes of group13 trihydrides and trihalides. It was found that the MH_3 fragments form mono-NHC four-coordinate complexes, with the ligand bridging two metal centres, whereas with $InBr_3$ and $TlCl_3$ the bis-NHC ligand coordinates in a chelating fashion .[18]



Scheme 7.

- The same group also reported on the reaction of GaI and InCl with mono-NHCs. A product was isolated using GaI only when it was reacted with a bulky NHC, and resulted in an anionic complex.[19]The gallium-NHC bond length is of 2.070 $A^{0.}$

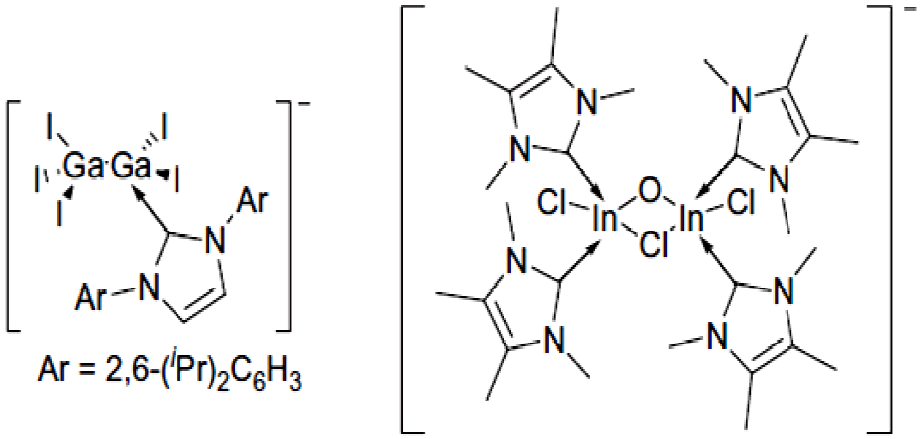
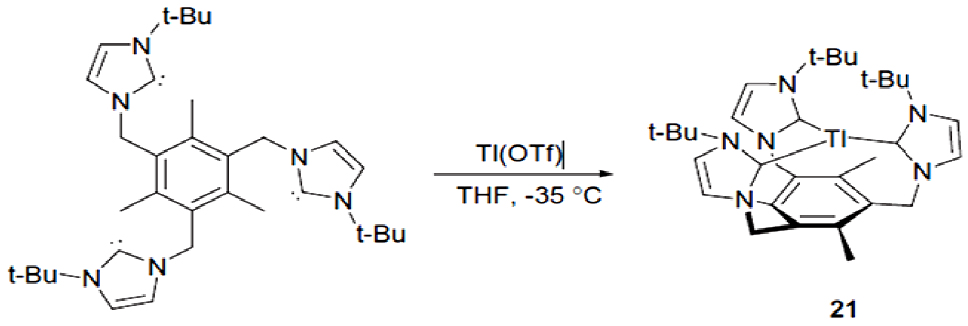


Fig.7

- In 2003, Mayer et *al.* reported first example of thallium-NHC, where a tris NHC ligand coordinated with metal. This thallium-tris-NHC complex present in tridentate conformation. The three carbene ligands are not symmetrically bound to the thallium as they exhibit slightly different thallium-NHC bond distances, with an average bond length of 2.952A ° .[20]



Scheme 8.

- Arduengo et *al.* in 1993 reported a Germanium-NHC complex. The most interesting feature of this compound is that the geometry around the germanium centre is pyramidal, with a germanium-NHC bond distance of 2.102(12)A ˚ . This is quite different to the geometry of a germaethene where the germanium and carbon atoms exhibit trigonal planar coordination and a shorter germanium-carbon bond length of 1.803A ˚.[21]

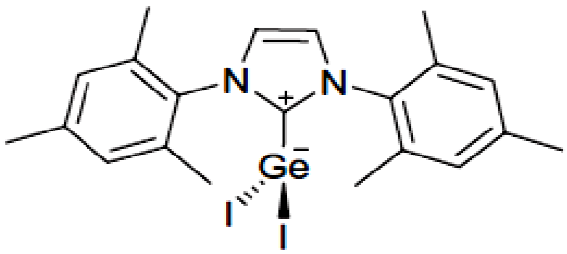
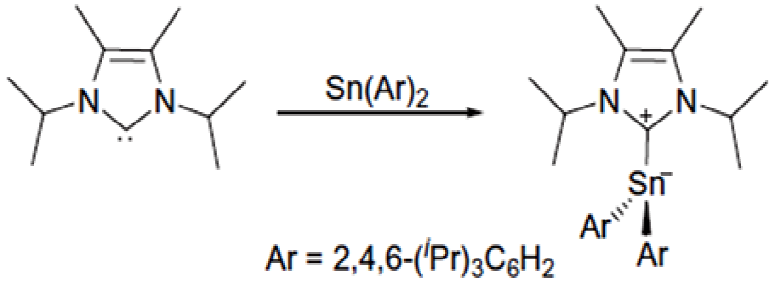


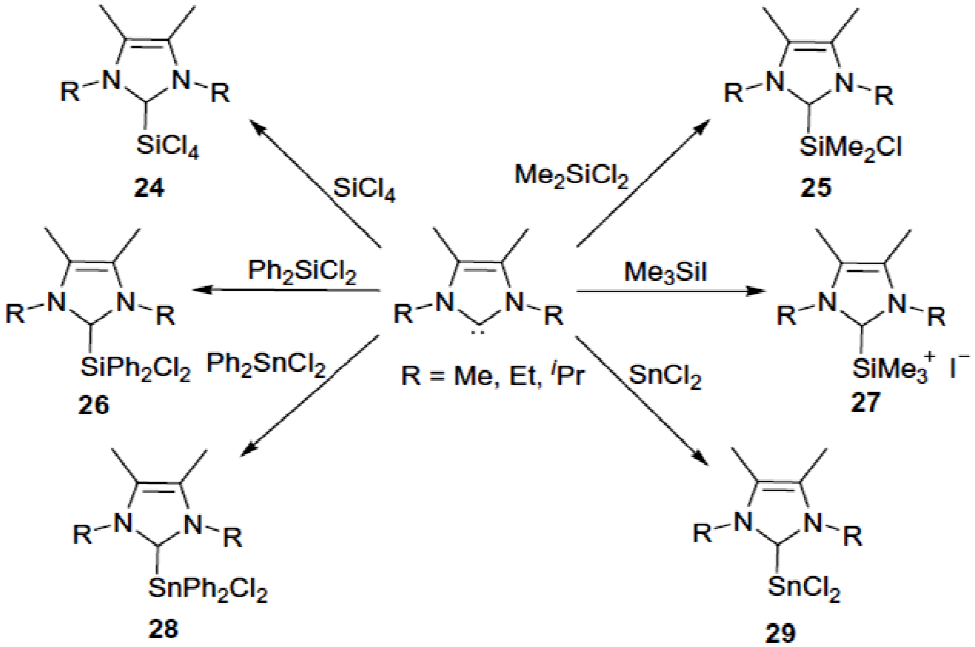
Fig.8

- A similar pyramidal structure was reported two years later by same group of researcher where a stable carbene was reacted with bis(2,4,6-triisopropylpheny1)stannylene.[22] The C2 carbon of the complex 23 is shifted upfield in the 13C NMR spectrum compared to the uncoordinated carbene, though only by 28 ppm which is significantly less than in the germanium adduct 22. The solid state structure has a tin-NHC bond length of 2.379(5)A ˚ .



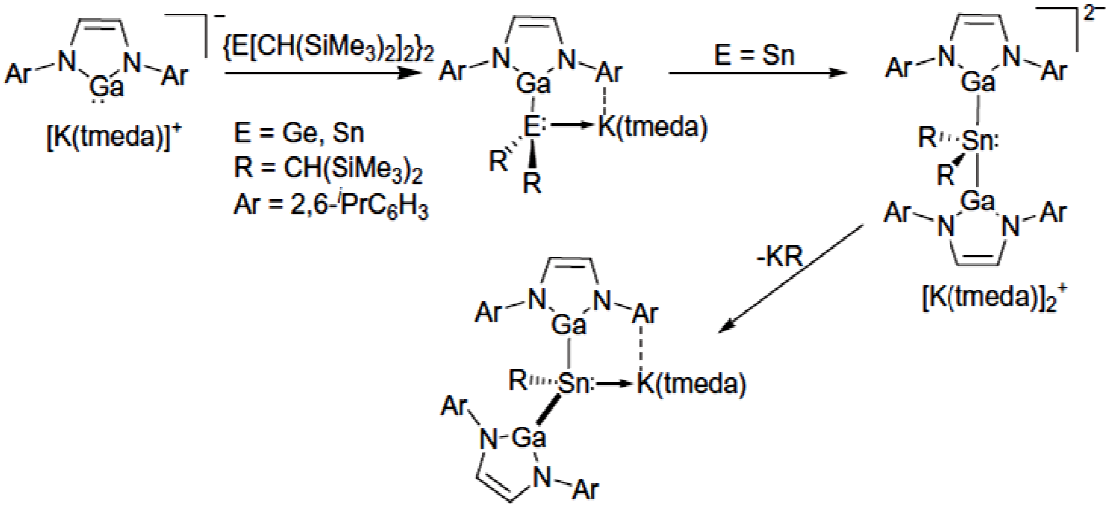
Scheme 9.

- Kuhn and co-workers reported a series of silicon- and tin-NHC complexes.The pentacordinated silicon and tin structures were determined by single crystal X-ray crystallography.[23] The pentacordinated silicon and tin structures 24 and 28 were determined by single crystal X-ray crystallography, and possess metal-NHC bond lengths of 1.911(7)A ˚ and 2.179(3)A respectively. The monomeric stannylene complex 29 was also characterised by single crystal X-ray crystallography and has a tin-NHC bond distance of 2.290(5)A.
- The NMR spectral data indicate significant Cþ–Si_ bond polarity and DFT calculations are also consistent with this.



Scheme 10.

- In 2006, Jones and co-workers reported the reaction of anionic gallium(I)-NHC analogues with the heavier group 14 (E) alkene analogues. The complexes formed exhibit long gallium-E bonds with that of E=Sn being 2.7186(6)A.[24]
- DFT calculations further comfirms the nature of the gallium-E bond and it was shown to be closely related to the neutral NHC adducts of group 14 dialkyls.



Scheme 11

NHCs Complexes of Copper and their Use as Catalyst-

Copper-mediated catalysis has become a burgeoning field of research. Similarly, the realized benefit of N-heterocyclic carbenes (NHC) as ancillary ligands in organometallic catalysis has led to significant advances over the last two decades[25]

In 1993, the first example of NHC-ligated copper was reported by Arduengo and took the form of a cationic di-carbene complex (Fig. 9) .[26]

Fig .9

The strong electronic donating properties of NHCs in conjunction with copper, yields catalyst that are often very robust, demonstrating air, moisture and thermal stability.

Cu NHCs complexes can be divided in to two major classes: neutral mono-NHC and cationic bis-NHC derivatives: [Cu(X)(NHC)] [27] (X = halide, acetate, hydroxide, hydride, etc.) and [Cu(NHC)(L)][Y] (L = NHC or PR3; Y = PF6, BF4) [28]

The first Cu–NHC mediated catalysis report was communicated in 2001, when Woodward reported that a solution of Cu(OTf)2, imidazolium salt and KOt Bu effectively catalyzed the conjugate addition of ZnEt2 to enones.[29] (Fig. 10).

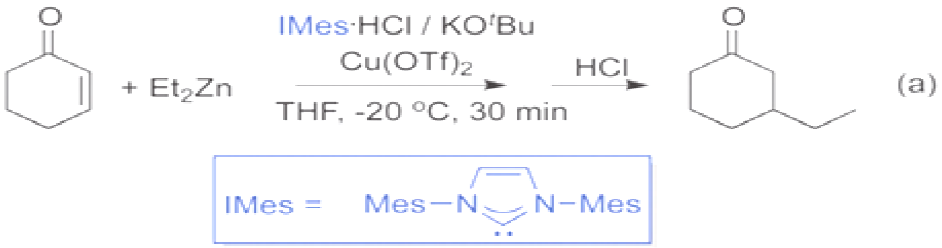


Fig .10

In 2003, Buchwald and Sadighi reported the first use of a well-defined Cu–NHC complex in catalysis (Fig. 11).[30] Using the newly reported IPr9 N,N0 -bis(2,6-diisopropylphenyl)imidazol-2-ylidene derivative of Raubenheimer's complex, the conjugate reduction of a,b-unsaturated carbonyl compounds was carried out

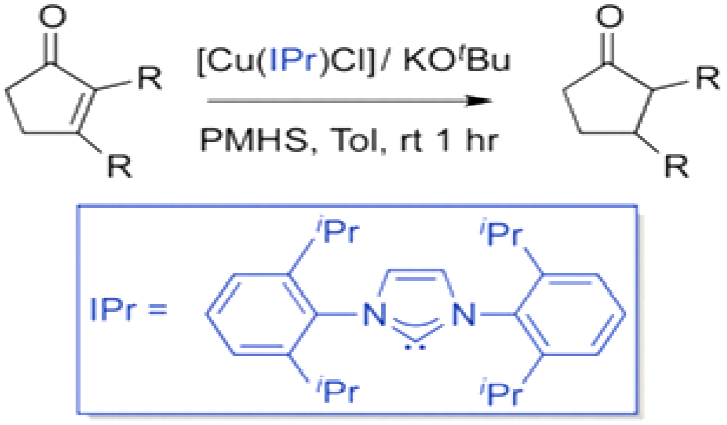


Fig 11

- In 2013, a dual catalysis 1,4-reduction/allylation process involving copper and palladium was reported by Riant and Nahra. In this case, [Cu(Cl)(IMes)] was selected for the 1,4-reduction reaction [31]. In the presence of a palladium complex, the allylic alkylation occurred leading to an interesting range of functional molecules.

- **Neutral [Cu(NHC)X]**- Cu–NHC complexes are very efficient in Hydrosilylation of carbonyl containing compounds. Nolan reported the ability of the [Cu(IPr)Cl][32] compound to catalyze the hydrosilylation of carbonyl complexes.(fig.12)

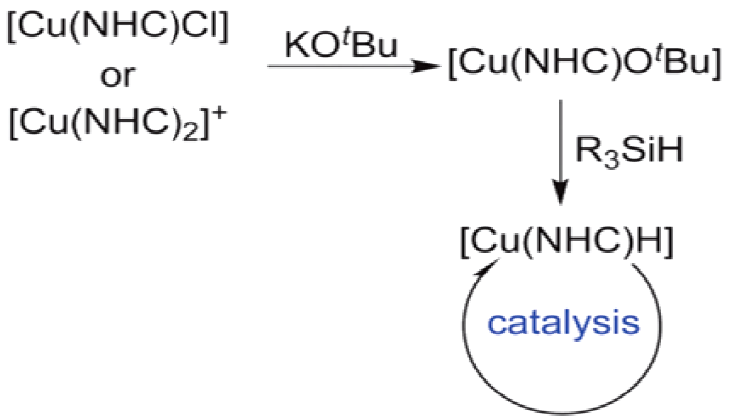


Fig.12

- **Cationic [Cu(NHC)2]$^{+}$ -** In 2006, the first structurally characterized cationic bis-imidiazolium carbene copper complex was synthesized.16 Again hydrosilylation reactions were performed and again the ICy-containing complex proved to be the most efficient catalyst.[33,34]**(fig .12)**

2.2 Biological Applications of NHCs Metal Complexes

The newly emerging interest in the medicinal applications of stable metal NHCs led us to examine the few accounts available in the literature dealing with this area of research. This review will discuss in detail the medicinal applications of various transition metal-NHC complexes including silver, gold, rhodium, ruthenium, and palladium. The antimicrobial, antitumor, and resistance properties, along with proposed mechanisms of action to suppress the bacterial growth or proliferation of tumor cells will be discussed.

Imidazolium salts are often used as precursors to metal-NHC complexes, and are commonly one of the byproducts produced from the degradation of NHC metal complexes.[35] The antimicrobial activity was evaluated against Staphylococcus aureus,Gaffkya tetragena, Sarcina lutea, Klebsiella pneumoniae, Serratia, marcescens,Rhodothorula glutinis, and Bacillus subtilis. They explored the effects of lipophilic substituents, anions, and backbone substituents on the antimicrobial activity associated with a series of 1,3-diazolidinium salts (5) and the effect of ring size of pyrimidinium salts (6) as a comparison . The complexes were tested against a number of bacterial organisms including E. coli, S. epidermidis, S. aureus, E. faecalis, E. cloacae, P. aeruginosa, and C. albicans and were compared to ampicillin, a β-lactam antibiotic used to treat

general bacterial infections. The imidazolidinium salts were much more active than the pyrimidinium salts.[36]

The antimicrobial activity studies of the new synthesized NHC silver complexes were investigated according to the recommended agar dilution procedure.[37] The minimal inhibitory concentrations (MICs) for each silver (I) complex were tested against standard bacterial strains (*E. faecalis*, *S. aureus*, *P. aeruginosa*, and *E. coli*) and fungal strains (*C.tropicalis* and *C. albicans*). NHC silver complexes were observed to have higher activity against fungal strains than against Gram-positive and Gram negative bacterial strains.

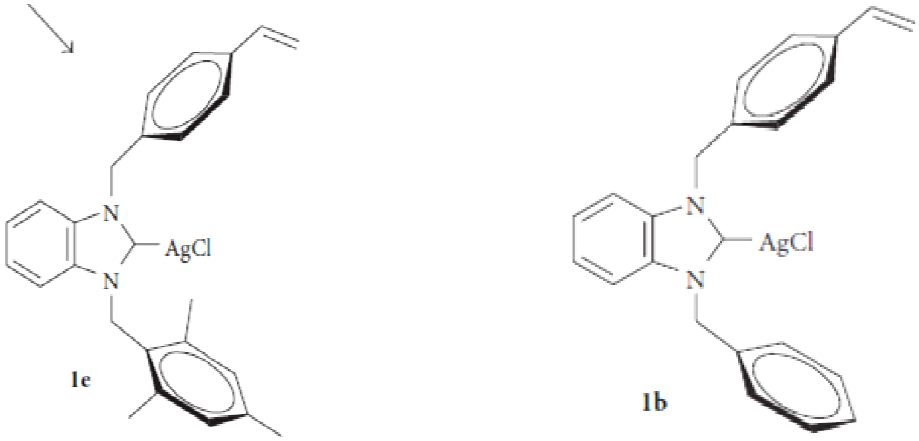


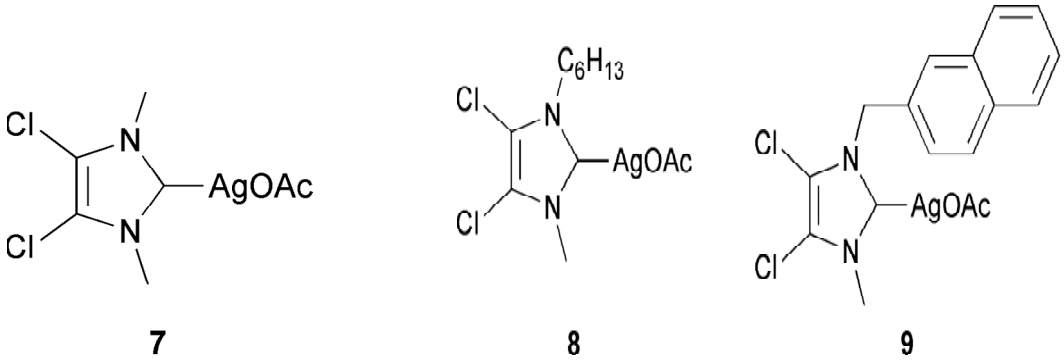
Fig.13

Anti-cancer properties

Nowadays, compounds of wide structural diversity are used as therapeutic agents for cancer treatment. The discovery of the antitumour properties of *cis*-platin by Rosenberg showed that not only drugs composed of the basic elements of the periodic table (carbon, oxygen, nitrogen) but also those containing heavy element may be toxic for tumour cells.[38]

Metal-NHCs are best known for their properties as catalysts,[39] however, the stability of the metal ligand bond has also recently allowed therapeutic investigations. Most of them can be found in the field of antimicrobials [40] but studies of their anti-cancer properties are also on-going.

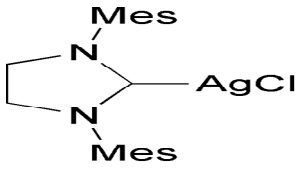
Silver salts have enjoyed a long history as antimicrobial agents and have proved to exhibit low toxicity for humans. **Youngs** and **colleagues** have also shown that the stability of Ag-NHC complexes was greatly enhanced by the addition of electron withdrawing groups on the 4 and 5 positions of the imidazole ring. All the chemical structures were based on a 4,5 dichloroimidazolydene core (**7**, **8** and **9**, Fig.7)



7 **8** **9**

Fig.14

The three Ag-NHC complexes tested were efficient on OVCAR-3 (ovarian) and MB157 (breast) cells, in the range of cisplatin. In the course of our studies on the anti-cancer properties of group 11 metal-NHC complexes, we determined the IC50 values for [AgCl(SIMes)] **11**, which is a full aromatic substituted carbene of high lipophilicity, on five human cancerous cell lines (KB: oral carcinoma, HL60: promyelocytic leukaemia, HL60R: resistant HL60, MCF7: breast cancer, MCF-7R: resistant MCF-7, T47D: breast cancer).[41] This complex inhibited the growth of all the different cell lines in a similar fashion.



11

Fig.15

The gold complexes shows potential as anticancer drug. Auranofin **16** and other gold(I) complexes of the general formula **17**, bearing the linear S-Au-PR3 moiety, were found to be more active than cisplatin Berners-Price's group then took advantage of the luminescence associated with aurophilic interactions in dinuclear gold(I)-NHC complex **20** to visualize its intracellular localization.[42.]

Recently, Berners-Price reported that homoleptic gold(I)-NHCs like **21** are inhibitors of Thioredoxin Reductase (TrxR; a selenoenzyme responsible for the regulation of the cell redox state) while being inactive toward glutathione reductase (GR).[43]

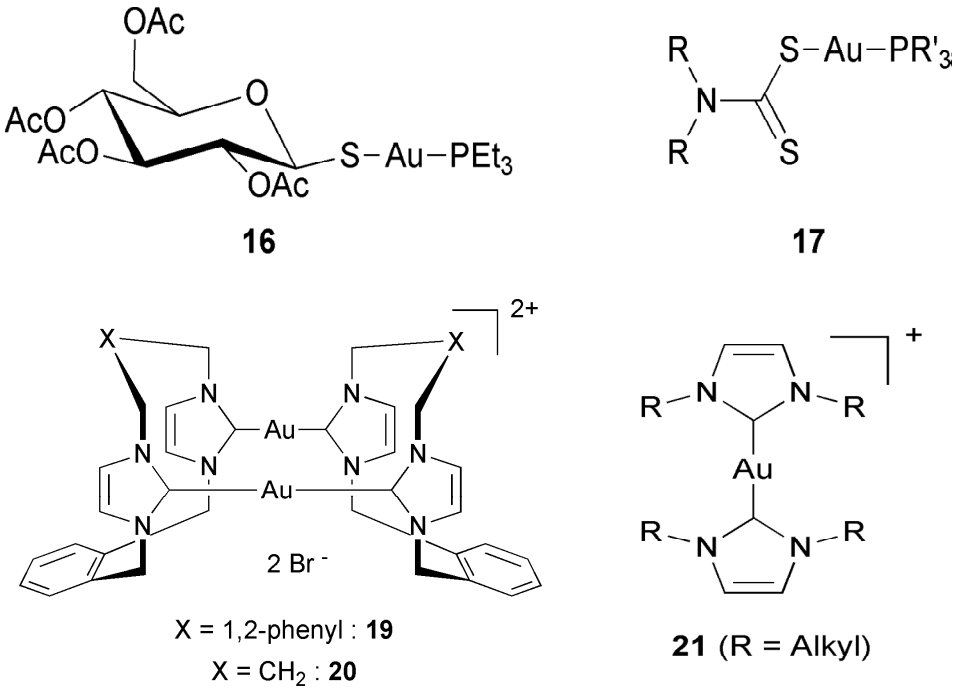


Fig.16

In the course of synthesizing metallo-drugs differing from cisplatin, exchange of the metal for palladium afforded compounds of higher cytotoxicities.[44]Interaction with DNA is a key feature of this type of complex. Panda and Ghosh reported the study of two kinds of Pd(II)-NHC complexes: one mixed complex **26**,withNHC and pyridine ligands. Complex **27** was the most potent inhibitor of the proliferation of HeLa cells: 85% inhibition at a 10 Mm concentration.

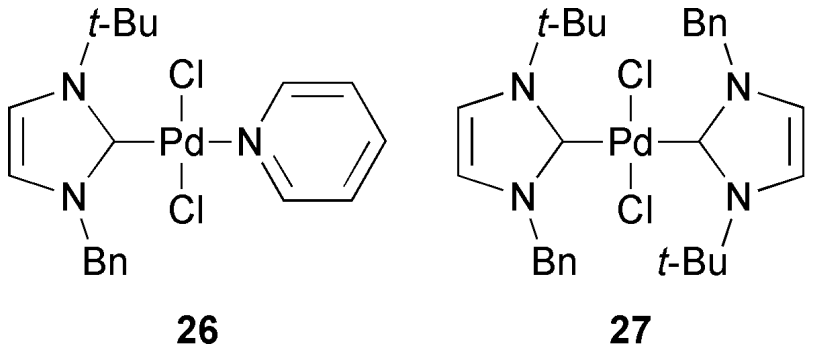
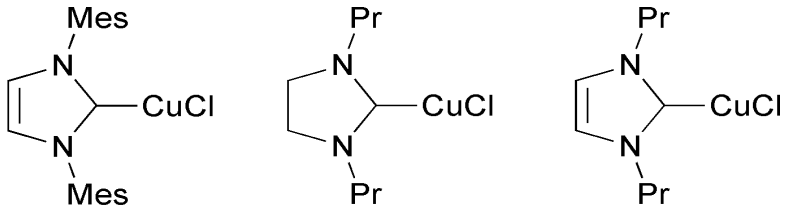


Fig.17

Among copper based anti-cancer agents,[45] most of the studies have focused on copper(II) complexes and their properties as chemical nucleases in the presence of oxygen and a reductant such as glutathione.[46]. A selected series of Cu-NHC complexes were synthesized according to their cytotoxicites and compared to cis platin.[47]



31 **32** **33**

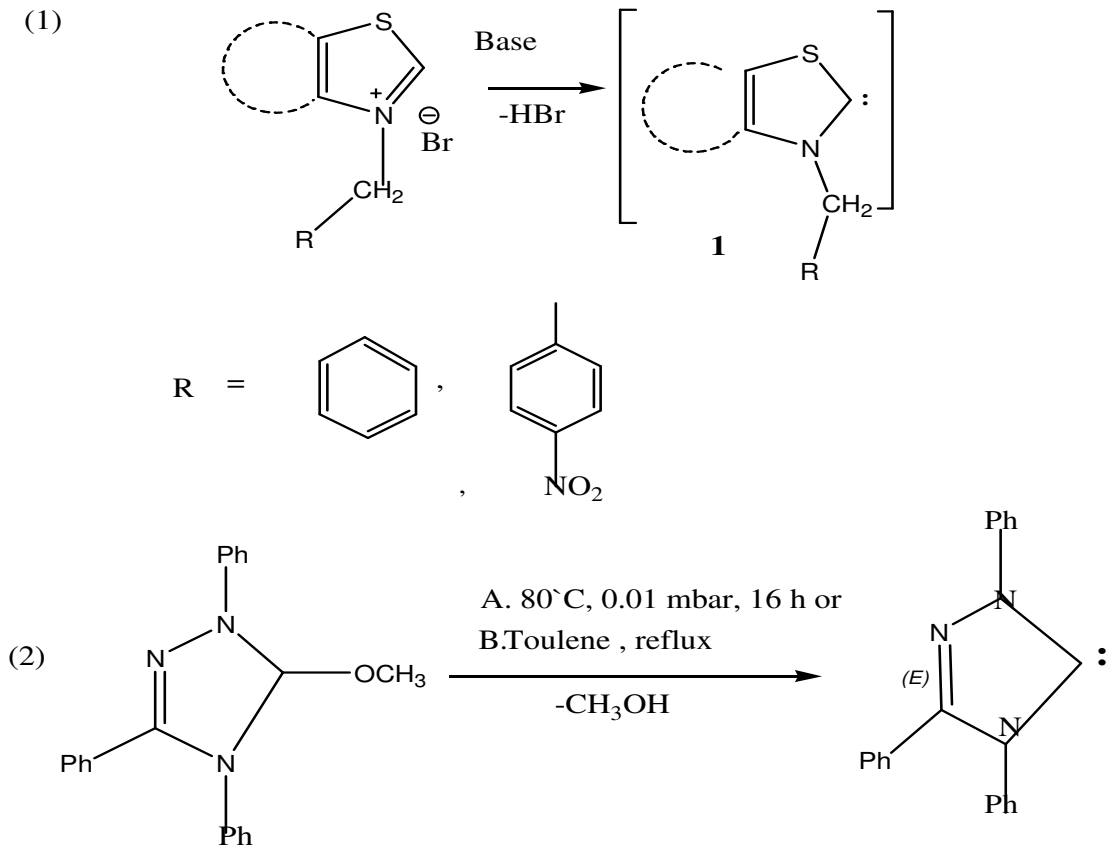
Fig.18

The organotin (IV) complexes showed strong cytotoxic activity (IC50 = 3.23–5.46 μM) than the parent ligand (IC50 = 6.20 μM) and standard drug, 5-Flourouracil (IC50 = 6.41 μM). As for the identical coordination geometry, the organotin(IV) complexes exhibited cytotoxic activity in the order of **[PhSnCl(L)] >[BuSnCl(L)] >[MeSnCl(L)].**

This study has been demonstrated that complex activity is dependent on the organo group attached to the metal centre in the order Ph > Bu> Me. This is might be due to the bulky organo group which increases lipophilicity of these complexes. Furthermore, phenyltin(IV) complex showed stronger cytotoxic activity than the other organotin(IV) derivatives. Between methyltin(IV) and butyltin(IV) complexes of H_2L ligand, complex showed stronger cytotoxic activity .[48]

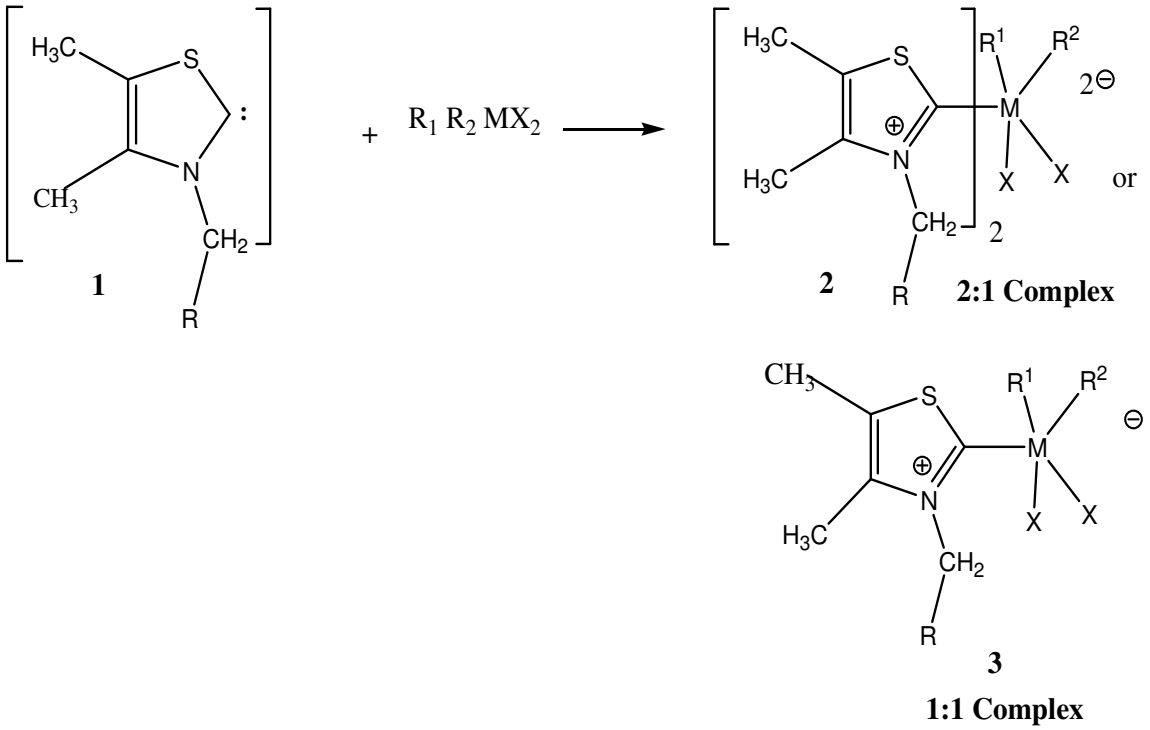
Objectives-

1. In situ generation of thiazolylidene and 1,2,4-Thiazolylidene carbenes.



Scheme 12

2. Preparation of tin (iv) complexes with the carbene as mentioned in the above scheme.



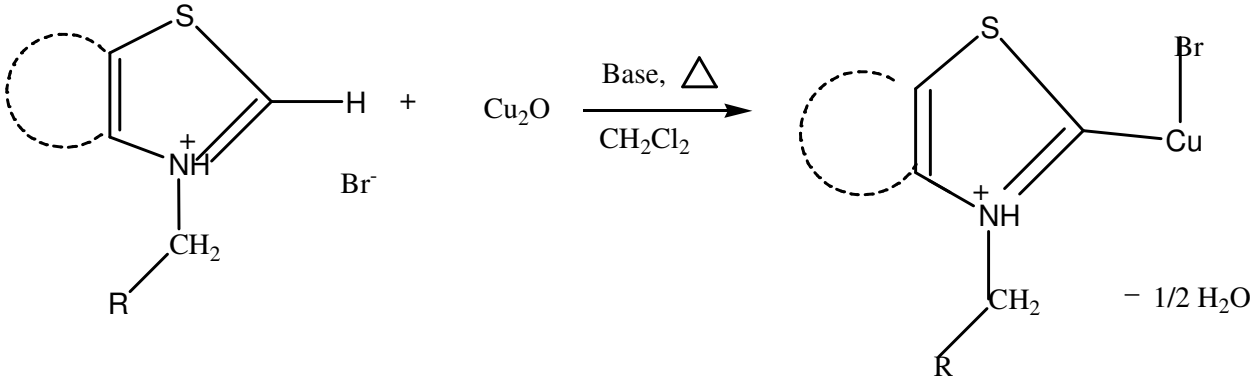
Scheme 13.

M = , Sn(IV),

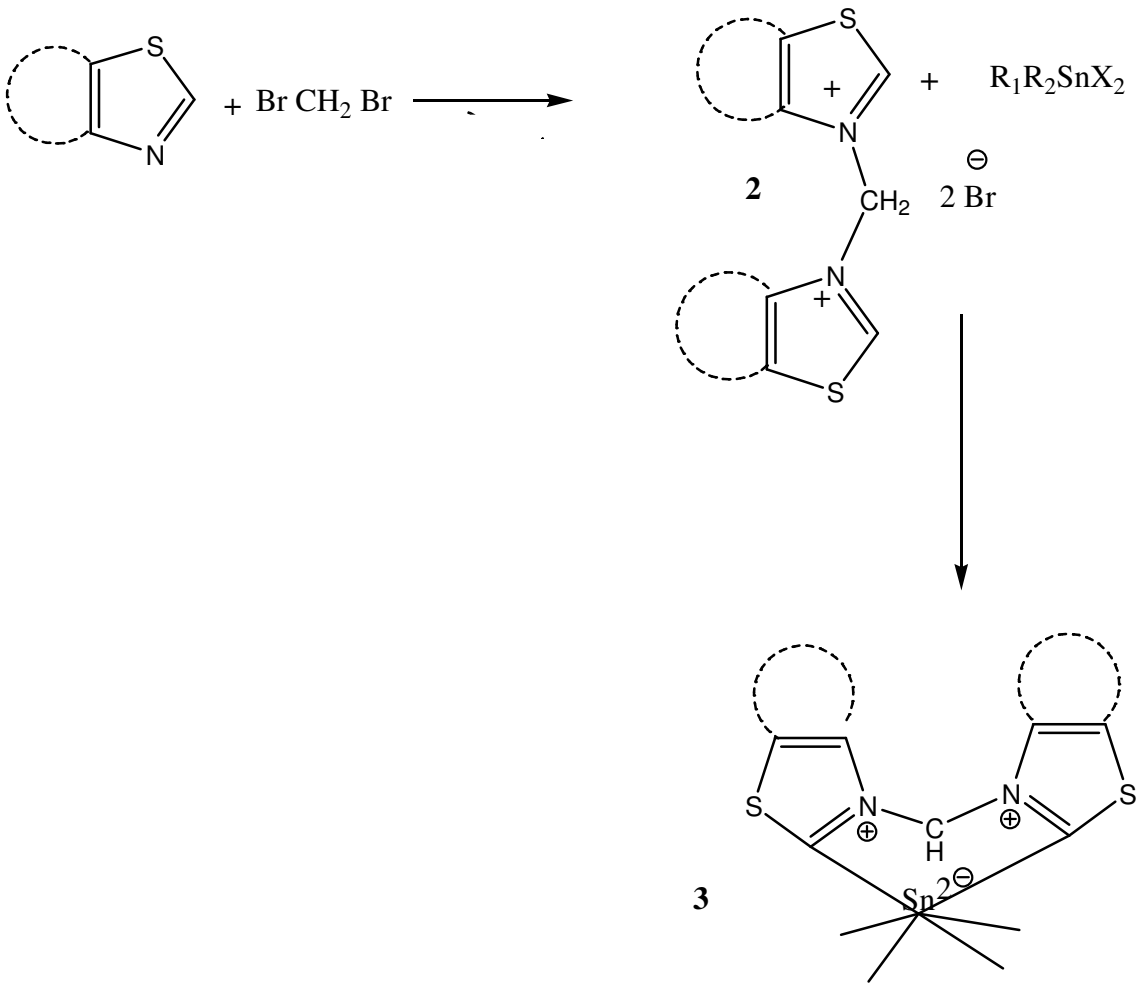
R^1,R^2 = Ph,Ph; Ph,Cl X_2 = Cl,Cl; Br,Br

R^1,R^2MX_2 = $SnCl_4$

3. . Preparation of Cu (II) complexes with the NHCs as mentioned in the above scheme.

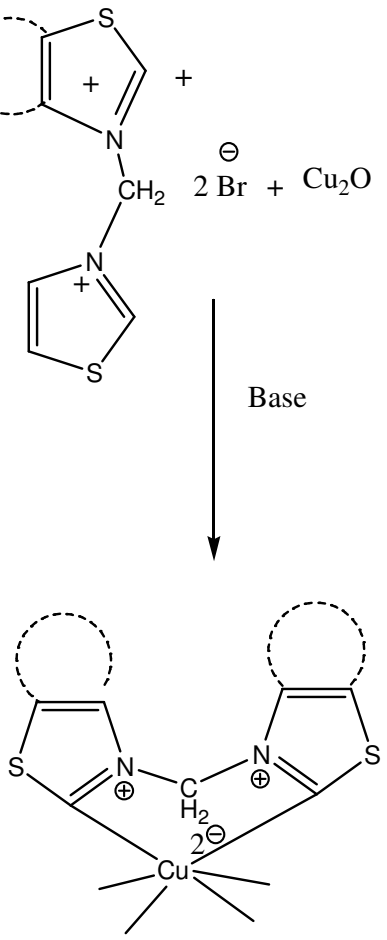


4. . Preparation of biscarbene complexes with tin(IV)



Scheme 14

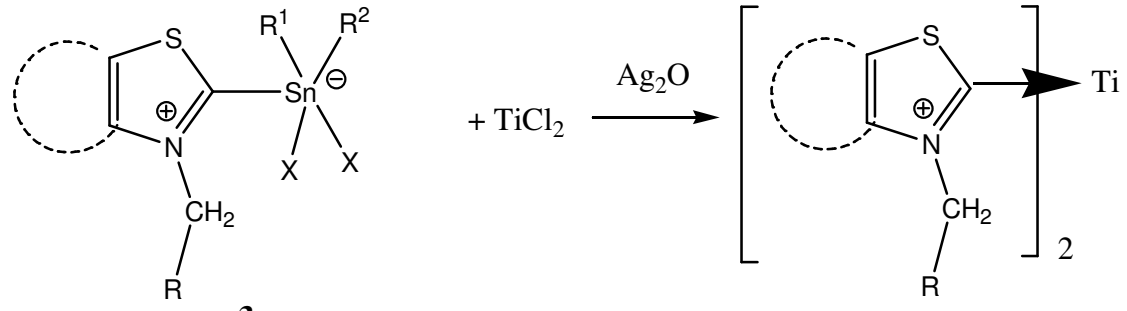
5. . Preparation of biscarbene complexes with Cu(II)



Scheme 15

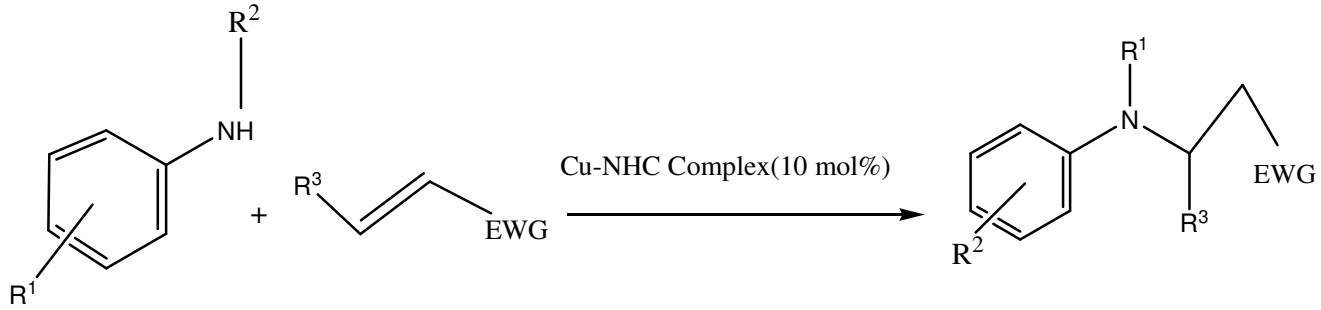
6. Characterization of the compounds by IR, ^{1}HNMR, ^{13}C NMR, ^{119}Sn NMR and X-Ray crystallography.

7. To use these complexes as carbene transfer reagents to prepare NHC transition metal complexes ($TiCl_4$).



Scheme 16

8. Use of Cu complexes as catalyst in Michael addition reaction.



R^1 = H, Me

R^2 = Me, OMe, NO_2

R^3 = Ph, Me

EWG = CN, CHO, CO_2Me

Scheme 17

9. Theoretical investigation of the optimized structure of the synthesized complexes.

10. To study biological activity of the tin carbene complexes.

Methodology

1. Preparation of Tin (IV) Complecxes generating carbene in situ

N-alkylthiazolium/ 1,2,4-Triazolium salt and alkyl halide was dissolved in dichloromethane(10mL) in 50 mL R.B flask and organotin compound (1eq) dissolved in dichloromethane was added to it and followed by the dropwise addition of triethylamine(1eq. in 2 mL dichloromethane) with continuous stirring at room temperature under nitrogen atmosphere. The resulting reaction mixture was allowed to stir for 2 days when a whitish pale /yellow product settle down.

The solvent was removed under reduced pressure and the resulting solid was extracted with THF(3x5 mL). The THF extract was concentrated to about 1/3 of its volume and left in refrigerator when colourless crystal will be obtained.

2. Preparation of Cu (IV) Complecxes generating carbene in situ

N-alkylthiazolium/ 1,2,4-Triazolium salt and alkyl halide was dissolved in dichloromethane(10mL) in 50 mL R.B flask and copper compound (1eq) dissolved in dichloromethane was added to it and followed by the dropwise addition of triethylamine(1eq. in 2 mL dichloromethane) with continuous stirring at room temperature under nitrogen atmosphere. The resulting reaction mixture was allowed to stir for 2 days when a whitish pale /yellow product settle down.

The solvent was removed under reduced pressure and the resulting solid was extracted with THF(3x5 mL). The THF extract was concentrated to about 1/3 of its volume and left in refrigerator when colourless crystal will be obtained.

3. Characterization of the products

The synthesized products (ligands and complexes) will be characterized by IR, ^{1}HNMR, ^{13}C NMR and ^{119}SnNMR. The structure of the complexes will be determined by X-ray crystallography.

4. Antibacterial activity

The synthesized complexes will be screened for biocidal activities. (kirby-bauer-Disk Diffusion Susceptibility test for antibacterial activity)

5 .Computational calculations

For computational calculations Gaussian 16. suite a programmes along with other softwares namely Gauss view 06, Molden, Chemcraft will be used.

Expected Achievements

It is expected that the proposed project will lead to the synthesis of some new tin(IV) NHC's complexes whose structures may exhibit some characteristic features expected in the complexes with NHC. Besides, the resulting compounds may exhibit interesting biological activities.

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